

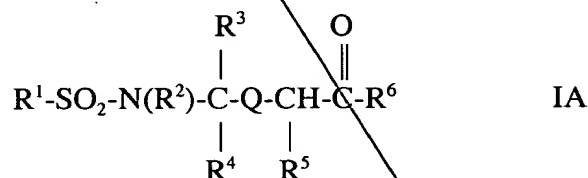
A³
B¹
cont

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is $=CH-X$ then (H) is removed from the formula and X is not hydroxyl;

Q is $-C(X)NR^7$ - wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur; or pharmaceutically acceptable salts thereof.

2. (Amended) A compound of formula IA below:



where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

A³
B²
R⁵ is selected from the group consisting of isopropyl, -CH₂X and =CH-X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R⁵ is =CH-X then (H) is removed from the formula and X is not hydroxyl;

R⁶ is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3- β -yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, -NH(CH₂)_pCOOY where *p* is an integer of from 1 to 8 and Y is as defined above, -OCH₂NR⁹R¹⁰ where R⁹ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R¹⁰ is selected from the group consisting of hydrogen and -CH₂COOR¹¹ where R¹¹ is alkyl, and -NHSO₂Z where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof

with the proviso that

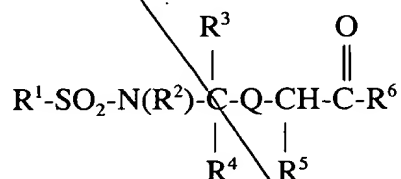
when R¹ is *p*-methylphenyl, R² and R³ are joined together with the nitrogen atom pendent to R² and the carbon atom pendent to R³ to form a pyrrolidinyl ring, R⁴ is methyl, R⁵ is *p*-hydroxybenzyl then R⁶ is not *t*-butoxy.

Cancel Claims 5-6 without prejudice.

A4
7. (Amended) The compound according to Claims 1 or 2 wherein R² and R³ together with the nitrogen atom bound to R² substituent and the carbon bound to the R³ substituent form a substituted heterocyclic ring.

Cancel Claims 8-9, 11 and 14 without prejudice.

A5
pub
B2
16. (Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



where

R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ form a heterocyclic or a substituted heterocyclic group;

R⁴ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R⁵ is selected from the group consisting of isopropyl, -CH₂X and =CH-X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R⁵ is

Q5
B2
cont
~~=CH-X then (H) is removed from the formula and X is not hydroxyl;~~

~~R⁶ is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), hydroxyl, amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, -NH(CH₂)_pCOOY where p is an integer of from 1 to 8 and Y is as defined above, -OCH₂NR⁹R¹⁰ where R⁹ is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R¹⁰ is selected from the group consisting of hydrogen and -CH₂COOR¹¹ where R¹¹ is alkyl, and -NHSO₂Z where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;~~

~~Q is -C(X)NR⁷- wherein R⁷ is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;~~

~~or pharmaceutically acceptable salts thereof~~

~~with the proviso that~~

~~when R¹ is *p*-methylphenyl, R² and R³ are joined together with the nitrogen atom pendent to R² and the carbon atom pendent to R³ to form a pyrrolidinyl ring, R⁴ is methyl, R⁵ is *p*-hydroxybenzyl then R⁶ is not *t*-butoxy.~~

Q6
B3
18. (Amended) The method according to Claim 17 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

Q7
19. (New) The method according to Claim 18 wherein said diabetes is acute juvenile onset diabetes.

a⁷ 20. (New) The method according to Claim 18 wherein said inflammatory bowel disease is ulcerative colitis or Crohn's disease.

21. (New) The method according to Claim 18 wherein said cerebral trauma is stroke.

22. (New) A compound selected from the group consisting of:

Push
C4
22 *23* *24* *25* *26* *27* *28* *29* *30* *31* *32* *33* *34* *35* *36* *37* *38* *39* *40* *41* *42* *43* *44* *45* *46* *47* *48* *49* *50* *51* *52* *53* *54* *55* *56* *57* *58* *59* *60* *61* *62* *63* *64* *65* *66* *67* *68* *69* *70* *71* *72* *73* *74* *75* *76* *77* *78* *79* *80* *81* *82* *83* *84* *85* *86* *87* *88* *89* *90* *91* *92* *93* *94* *95* *96* *97* *98* *99* *100* *101* *102* *103* *104* *105* *106* *107* *108* *109* *110* *111* *112* *113* *114* *115* *116* *117* *118* *119* *120* *121* *122* *123* *124* *125* *126* *127* *128* *129* *130* *131* *132* *133* *134* *135* *136* *137* *138* *139* *140* *141* *142* *143* *144* *145* *146* *147* *148* *149* *150* *151* *152* *153* *154* *155* *156* *157* *158* *159* *160* *161* *162* *163* *164* *165* *166* *167* *168* *169* *170* *171* *172* *173* *174* *175* *176* *177* *178* *179* *180* *181* *182* *183* *184* *185* *186* *187* *188* *189* *190* *191* *192* *193* *194* *195* *196* *197* *198* *199* *200* *201* *202* *203* *204* *205* *206* *207* *208* *209* *210* *211* *212* *213* *214* *215* *216* *217* *218* *219* *220* *221* *222* *223* *224* *225* *226* *227* *228* *229* *230* *231* *232* *233* *234* *235* *236* *237* *238* *239* *240* *241* *242* *243* *244* *245* *246* *247* *248* *249* *250* *251* *252* *253* *254* *255* *256* *257* *258* *259* *260* *261* *262* *263* *264* *265* *266* *267* *268* *269* *270* *271* *272* *273* *274* *275* *276* *277* *278* *279* *280* *281* *282* *283* *284* *285* *286* *287* *288* *289* *290* *291* *292* *293* *294* *295* *296* *297* *298* *299* *300* *301* *302* *303* *304* *305* *306* *307* *308* *309* *310* *311* *312* *313* *314* *315* *316* *317* *318* *319* *320* *321* *322* *323* *324* *325* *326* *327* *328* *329* *330* *331* *332* *333* *334* *335* *336* *337* *338* *339* *340* *341* *342* *343* *344* *345* *346* *347* *348* *349* *350* *351* *352* *353* *354* *355* *356* *357* *358* *359* *360* *361* *362* *363* *364* *365* *366* *367* *368* *369* *370* *371* *372* *373* *374* *375* *376* *377* *378* *379* *380* *381* *382* *383* *384* *385* *386* *387* *388* *389* *390* *391* *392* *393* *394* *395* *396* *397* *398* *399* *400* *401* *402* *403* *404* *405* *406* *407* *408* *409* *410* *411* *412* *413* *414* *415* *416* *417* *418* *419* *420* *421* *422* *423* *424* *425* *426* *427* *428* *429* *430* *431* *432* *433* *434* *435* *436* *437* *438* *439* *440* *441* *442* *443* *444* *445* *446* *447* *448* *449* *450* *451* *452* *453* *454* *455* *456* *457* *458* *459* *460* *461* *462* *463* *464* *465* *466* *467* *468* *469* *470* *471* *472* *473* *474* *475* *476* *477* *478* *479* *480* *481* *482* *483* *484* *485* *486* *487* *488* *489* *490* *491* *492* *493* *494* *495* *496* *497* *498* *499* *500* *501* *502* *503* *504* *505* *506* *507* *508* *509* *510* *511* *512* *513* *514* *515* *516* *517* *518* *519* *520* *521* *522* *523* *524* *525* *526* *527* *528* *529* *530* *531* *532* *533* *534* *535* *536* *537* *538* *539* *540* *541* *542* *543* *544* *545* *546* *547* *548* *549* *550* *551* *552* *553* *554* *555* *556* *557* *558* *559* *560* *561* *562* *563* *564* *565* *566* *567* *568* *569* *570* *571* *572* *573* *574* *575* *576* *577* *578* *579* *580* *581* *582* *583* *584* *585* *586* *587* *588* *589* *590* *591* *592* *593* *594* *595* *596* *597* *598* *599* *600* *601* *602* *603* *604* *605* *606* *607* *608* *609* *610* *611* *612* *613* *614* *615* *616* *617* *618* *619* *620* *621* *622* *623* *624* *625* *626* *627* *628* *629* *630* *631* *632* *633* *634* *635* *636* *637* *638* *639* *640* *641* *642* *643* *644* *645* *646* *647* *648* *649* *650* *651* *652* *653* *654* *655* *656* *657* *658* *659* *660* *661* *662* *663* *664* *665* *666* *667* *668* *669* *670* *671* *672* *673* *674* *675* *676* *677* *678* *679* *680* *681* *682* *683* *684* *685* *686* *687* *688* *689* *690* *691* *692* *693* *694* *695* *696* *697* *698* *699* *700* *701* *702* *703* *704* *705* *706* *707* *708* *709* *710* *711* *712* *713* *714* *715* *716* *717* *718* *719* *720* *721* *722* *723* *724* *725* *726* *727* *728* *729* *730* *731* *732* *733* *734* *735* *736* *737* *738* *739* *740* *741* *742* *743* *744* *745* *746* *747* *748* *749* *750* *751* *752* *753* *754* *755* *756* *757* *758* *759* *760* *761* *762* *763* *764* *765* *766* *767* *768* *769* *770* *771* *772* *773* *774* *775* *776* *777* *778* *779* *780* *781* *782* *783* *784* *785* *786* *787* *788* *789* *790* *791* *792* *793* *794* *795* *796* *797* *798* *799* *800* *801* *802* *803* *804* *805* *806* *807* *808* *809* *810* *811* *812* *813* *814* *815* *816* *817* *818* *819* *820* *821* *822* *823* *824* *825* *826* *827* *828* *829* *830* *831* *832* *833* *834* *835* *836* *837* *838* *839* *840* *841* *842* *843* *844* *845* *846* *847* *848* *849* *850* *851* *852* *853* *854* *855* *856* *857* *858* *859* *860* *861* *862* *863* *864* *865* *866* *867* *868* *869* *870* *871* *872* *873* *874* *875* *876* *877* *878* *879* *880* *881* *882* *883* *884* *885* *886* *887* *888* *889* *890* *891* *892* *893* *894* *895* *896* *897* *898* *899* *900* *901* *902* *903* *904* *905* *906* *907* *908* *909* *910* *911* *912* *913* *914* *915* *916* *917* *918* *919* *920* *921* *922* *923* *924* *925* *926* *927* *928* *929* *930* *931* *932* *933* *934* *935* *936* *937* *938* *939* *940* *941* *942* *943* *944* *945* *946* *947* *948* *949* *950* *951* *952* *953* *954* *955* *956* *957* *958* *959* *960* *961* *962* *963* *964* *965* *966* *967* *968* *969* *970* *971* *972* *973* *974* *975* *976* *977* *978* *979* *980* *981* *982* *983* *984* *985* *986* *987* *988* *989* *990* *991* *992* *993* *994* *995* *996* *997* *998* *999* *1000* *1001* *1002* *1003* *1004* *1005* *1006* *1007* *1008* *1009* *1010* *1011* *1012* *1013* *1014* *1015* *1016* *1017* *1018* *1019* *1020* *1021* *1022* *1023* *1024* *1025* *1026* *1027* *1028* *1029* *1030* *1031* *1032* *1033* *1034* *1035* *1036* *1037* *1038* *1039* *1040* *1041* *1042* *1043* *1044* *1045* *1046* *1047* *1048* *1049* *1050* *1051* *1052* *1053* *1054* *1055* *1056* *1057* *1058* *1059* *1060* *1061* *1062* *1063* *1064* *1065* *1066* *1067* *1068* *1069* *1070* *1071* *1072* *1073* *1074* *1075* *1076* *1077* *1078* *1079* *1080* *1081* *1082* *1083* *1084* *1085* *1086* *1087* *1088* *1089* *1090* *1091* *1092* *1093* *1094* *1095* *1096* *1097* *1098* *1099* *1100* *1101* *1102* *1103* *1104* *1105* *1106* *1107* *1108* *1109* *1110* *1111* *1112* *1113* *1114* *1115* *1116* *1117* *1118* *1119* *1120* *1121* *1122* *1123* *1124* *1125* *1126* *1127* *1128* *1129* *1130* *1131* *1132* *1133* *1134* *1135* *1136* *1137* *1138* *1139* *1140* *1141* *1142* *1143* *1144* *1145* *1146* *1147* *1148* *1149* *1150* *1151* *1152* *1153* *1154* *1155* *1156* *1157* *1158* *1159* *1160* *1161* *1162* *1163* *1164* *1165* *1166* *1167* *1168* *1169* *1170* *1171* *1172* *1173* *1174* *1175* *1176* *1177* *1178* *1179* *1180* *1181* *1182* *1183* *1184* *1185* *1186* *1187* *1188* *1189* *1190* *1191* *1192* *1193* *1194* *1195* *1196* *1197* *1198* *1199* *1200* *1201* *1202* *1203* *1204* *1205* *1206* *1207* *1208* *1209* *1210* *1211* *1212* *1213* *1214* *1215* *1216* *1217* *1218* *1219* *1220* *1221* *1222* *1223* *1224* *1225* *1226* *1227* *1228* *1229* *1230* *1231* *1232* *1233* *1234* *1235* *1236* *1237* *1238* *1239* *1240* *1241* *1242* *1243* *1244* *1245* *1246* *1247* *1248* *1249* *1250* *1251* *1252* *1253* *1254* *1255* *1256* *1257* *1258* *1259* *1260* *1261* *1262* *1263* *1264* *1265* *1266* *1267* *1268* *1269* *1270* *1271* *1272* *1273* *1274* *1275* *1276* *1277* *1278* *1279* *1280* *1281* *1282* *1283* *1284* *1285* *1286* *1287* *1288* *1289* *1290* *1291* *1292* *1293* *1294* *1295* *1296* *1297* *1298* *1299* *1300* *1301* *1302* *1303* *1304* *1305* *1306* *1307* *1308* *1309* *1310* *1311* *1312* *1313* *1314* *1315* *1316* *1317* *1318* *1319* *1320* *1321* *1322* *1323* *1324* *1325* *1326* *1327* *1328* *1329* *1330</*

Q7
Q4
cont
~~*N*-(toluene-4-sulfonyl)- α -methylprolyl-D-tyrosine *tert*-butyl ester;~~

~~*N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenyl-
alanine 1-(trimethyacetoxymethyl ester;~~

~~*N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-[*N*-(2-(*N*',*N*'-dimethylamino)ethyl)-*N*-
methylcarbamyloxy]phenylalanine *tert*-butyl ester;~~

~~*N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-[*N*-(2-(*N*',*N*'-dimethylamino)ethyl)-*N*-
methylcarbamyloxy]phenylalanine;~~

~~*N*-(4-fluorobenzenesulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenyl-
alanine *tert*-butyl ester;~~

~~*N*-(4-fluorobenzenesulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenyl-
alanine~~

or pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester group is replaced with another ester group selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

REMARKS

Claim Status

Applicants respectfully request that the instant application be reconsidered in view of the above amendments and the following remarks. Claims 1-18 were pending in the application. Of these claims, the Examiner withdrew from consideration claims 5, 8, 9 and 11. Applicants request the cancellation of claims 5-6, 8-9, 11 and 14 and reserve the right to file applications directed to the canceled subject matter at a later date. Applicants further request the addition of claims 19-22. Upon entry of this Amendment, claims 1-4, 7, 12, 13, and 15-22 will be pending in the instant application.

Election/Restriction

Applicants respectfully acknowledge the Examiner's amendment of Group III to contain claims 1-4, 6-7, 10 and 12-18.